American Chemistry Council
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January 30, 2004

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Dr. Christopher Portier
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Research Triangle Park, NC 27709-2233

Re: National Toxicology Program's Public Meeting to Discuss the Review Process And the Listing/Delisting Criteria Used for the Report on Carcinogens

Dear Dr. Portier:

The American Chemistry Council is pleased to respond to the National Toxicology Program's (NTP's) request for comments on the Review Process and the Listing/Delisting Criteria Used for the Report on Carcinogens (68 FR 67692, Dec. 3, 2003). For over three decades the American Chemistry Council[1] (ACC) and its member companies have played an active role in screening and testing chemical substances, developing risk assessments and implementing science-based risk management policies. ACC supports NTP's research and testing efforts, and in particular encourages the use of more mechanistic data in hazard and risk assessments. The NTP's Reports on Carcinogens (RoCs) are both nationally and globally significant documents in the area of chemical assessment, and ACC thus welcomes – and commends NTP for initiating – this effort to ensure that progress is

[1] The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through health and environmental research and product testing, Responsible Care®, and common sense advocacy designed to address major public policy issues. The business of chemistry is a $460 billion enterprise and a key element of the nation's economy. It is the nation's largest exporter, accounting for ten cents out of every dollar in U.S. exports. Chemistry companies invest more in research and development than any other business sector. Safety and security have always been primary concerns of ACC members, and they have intensified their efforts, working closely with government agencies to improve security and to defend against any threat to the nation's critical infrastructure. As a science-driven industry, the business of chemistry – through the Council's Long Range Research Initiative and thorough research, screening and testing of specific chemicals by individual member companies – provides significant support for scientific research to better understand and characterize the potential risks from chemical exposures.

made to improve the RoC process. To that end, ACC offers the following comments and recommendations to improve the scientific accuracy and the transparency of the process. Specifically, ACC recommends that NTP:

- consider strengthening the scientific quality and public participation processes in the development of RoC actions by adapting and building on the process currently used by its own Center for the Evaluation of Risks to Human Reproduction (CERHR); and

- clarify the listing/delisting criteria it uses for the RoC to ensure that "a known to be a human carcinogen" determination is made only when there is sufficient epidemiological evidence of carcinogenicity from epidemiological or clinical studies that indicate a causal relationship, based on the weight of the scientific evidence, between exposure to the agent, substance or mixture and development of cancer in humans.

The basis for and the details of these recommendations are explained below.

1. Strengthening the Scientific Process: the Case for Qualitative Change

ACC and others have criticized the process and procedures followed by NTP to develop recommendations for listing chemicals in the RoC for many years[2]. Some of the major shortcomings of the RoC which have been previously communicated to NTP include:

- Failure to Prepare Up-to-Date, High-Quality Background Documents for Substances Recommended for Listing
- Too Little Time for the Preparation and Consideration of Scientific Comments on Listing Recommendations
- Insufficient Opportunity for Scientific Interchange with the Peer Review Body
- Failure to Involve Knowledgeable Outside Experts in Chemical-Specific Reviews
- NTP classifications that Differ From Those of Other Expert Scientific Bodies Without Clear Rationale or Justification
- Lack of Clear Guidance on the Standards That Need to Be Met for Listing Classifications and Use of the Term "Known Human Carcinogen" In The Absence Of Adequate Human Epidemiological Data

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[2] Such criticisms are not repeated in detail in these comments -- the intent here is provide thoughtful commentary on a path forward for NTP to consider undertaking to improve the RoC. Should NTP have need of copies of past ACC communications critiquing the RoC, NTP may contact ACC and these will be supplied.

- Absence of Documented Rationales for Decisions of the Interagency Review Group (RG-2), and the Board of Scientific Counselors (BSC) Subcommittee or the NTP Executive Committee

ACC believes that the process and procedures currently employed by NTP for the RoC do not compare favorably with the processes that other agencies and scientific review bodies follow in hazard evaluations of potential carcinogenic agents. The current RoC process still does not foster opportunities for substantive scientific dialogue among the most qualified chemical-specific and subject matter specific experts during the most critical stages of the process, including the comprehensive literature evaluation/writing and review of the Draft Background Review Document. There continue to be instances where the RoC work products could have benefited from the participation of well-recognized experts. Further, the RoC procedures for public/stakeholder participation fall well short of what is needed to demonstrate a commitment to truly meaningful participation. Even though extensive comments are often submitted highlighting new data or important mechanistic or interpretative information relevant to critical studies, the Background Review Document is typically not revised and there is no indication whether such comments are actually considered or addressed.

ACC acknowledges that NTP's efforts over the years to make incremental changes in the RoC process have led to incremental enhancements, but there are many areas that remain problematic, and both the scientific processes and the public/stakeholder procedures used by NTP -- even as proposed in the current FR notice -- are still in need of substantial improvement. To upgrade the NTP RoC process, the ACC suggests NTP consider implementing specific improvements, which are detailed below, to restore confidence in, and improve the scientific integrity of, the RoC process.

2. Strengthening the Scientific Process: Fundamental Principles

The foundation of RoC listings and delistings should be a comprehensive and thorough review and interpretation of the best available science, conducted in a manner that fosters scientific dialogue, transparent decision making, open meetings and stakeholder involvement. These are fundamental principles, widely supported by the NTP, other Federal agencies and departments, academia, industry and other stakeholders. In its review of the RoC process, NTP should be focused on ensuring that these fundamental principles are enhanced. Such a focus would also ensure that the RoC process comports with the Information Quality Act (IQA), including the peer review provisions that the Office of Management and Budget (OMB) has proposed to add to its IQA Guidelines. As the RoC process stands now, there is no doubt that it does not satisfy the OMB's peer review requirements for "especially significant regulatory information" like the RoCs. (For example, the peer reviewers do not prepare any sort of report of their deliberations.) Moreover, at least one substantial IQA challenge has been filed against the 10th RoC. Improvements to the RoC process would substantially reduce the likelihood of such challenges in the

future. Now is the time for NTP to consider more sweeping alternatives to the existing process.

Fortunately, with the CERHR, NTP itself has implemented a hazard characterization process that goes a long way to overcoming many of the scientific and process shortcomings of the current RoC process. ACC suggests that, as NTP considers potential reforms to the RoC process, it consider whether there are lessons to be learned from the process developed by its own CERHR. Figure 1 illustrates the current CERHR process, as described on the Center's website[3]. The CERHR process involves numerous opportunities for substantive public/stakeholder involvement, including the opportunitunities to:

- nominate substances,
- comment on nominated substances,
- comment on substances recommended for review,
- submit nominations of scientists to serve on the Expert Panels,
- comment on the Draft Expert Panel Report for each substance,
- participate in open and collegial, in-depth Expert Panel meetings, and
- comment on the final Expert Panel Report.

ACC urges NTP to consider adding the comparable opportunities for public/stakeholder interaction in a similar RoC listing and delisting process, as discussed below.

3. Strengthening the Scientific Process: NTP Should Consider Adapting the CERHR Process for the RoC

ACC believes that NTP's RoC process could be greatly improved by adapting and building on the interactive scientific model put into practice in the CERHR process. ACC suggests the following adaptation of the CERHR process for consideration by NTP as a possible revision to the RoC process (the proposed process is also illustrated in Figure 2):

- Listing & Delisting Nominations
    - Maintain an open nomination process which includes interested individuals, federal and state agencies, NTP staff, labor unions, and industry. Listing and delisting nominations may be accompanied by a dossier explaining the rationale and supporting data for the nomination.

- Nomination Review Committee
    - RoC staff prepares dossiers on candidate chemicals and supplies the dossiers to the Nomination Review Committee annually.

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[3] http://cerhr.niehs.nih.gov/aboutCERHR/index.html#Chemical%20Review%20Process

  - Nomination Review Committee reviews dossiers and recommends proposed candidate chemicals giving highest priority to chemicals nominated based on scientific evidence regarding the potential carcinogenicity of the nominated substance (taking into account potential for human exposure).
  - Proposed candidate chemicals (for either listing or delisting) transmitted to Associate Director, NTP who finalizes the list of proposed candidate chemicals for public comment.
- Solicitation of Public Comment on Agents Selected by the Associate Director of NTP
  - Federal Register notice announces selected chemical(s) and solicits public comment, new data and planned studies, information on exposure and use patterns, and nominations of individuals qualified to serve on the Expert Panel
- RoC Nomination Review Committee Review
  - Reviews expert panel member recommendations
  - Recommends Expert Panel members to Associate Director, NTP, for final approval
- Request for Scientific & Public Review/Comments and Development of Review Draft of Expert Panel Report
  - Federal Register notice announces the Expert Panel meeting and requests public comments to be submitted in writing and/or made at this meeting
  - Expert Panel Meeting to discuss dossier, receive scientific input from non-panelists, and public comments
  - Expert Panel participants review available scientific studies (dossier, other scientific data/studies/information and public comments) and prepare the Review Draft Expert Panel Report
- Expert Panel Meeting – Release of the Review Draft Expert Panel Report for comment
  - The Panel meets in public session to discuss its draft report (which would provide a comprehensive review of the literature) and to prepare the final Panel report
  - Meeting includes adequate time for presentation of public comments and for substantive interaction between commentators and panelists
- Request for Scientific & Public Review/Comments on Final Expert Panel Report
  - Federal Register notice announces availability of Expert Panel report and requests public comment. This report is a product of the Expert Panel and is available on the NTP website or from NTP
  - NTP RoC Peer Review Committee conducts peer review and provides written report on their deliberations (including a response to comments)
- NTP Draft Monograph
  - RoC staff prepares a Draft Monograph on the chemical(s) evaluated based on the Final Expert Panel Report

- Final Solicitation of Public Comments
  - Federal Register notice announces availability of Draft Monograph and requests public comments
- NTP Interagency Executive Committee Approval
  - The Draft Monograph is transmitted to the Interagency Executive Committee along with the final public comments for review and approval (to include a report on response to comments)
- Final Monograph Submitted to Director NTP and Secretary DHHS for Approval and Publication
  - RoC staff revises the Monograph as directed by the Interagency Executive Committee
  - Monograph (with chapter on response to comments) is transmitted to Director NTP for approval
  - Director NTP recommends approval to Secretary DHHS
  - The Monograph is made publicly available and is distributed to federal and state agencies and interested stakeholders

Clearly, such changes to the RoC as proposed for consideration would present new challenges to the NTP. While implementing a more open and transparent process that allows for enhancing scientific quality and dialogue may take more time than the current approach, this should be viewed as time well spent. Clearly, the initial work product of the Expert Panel would be greatly strengthened in terms of scientific rigor by implementing a process that includes recognized subject matter experts from a diverse array of applicable fields and affiliations working in a collaborative manner to develop the Background Review Document. As currently structured, the RoC process, particularly at the crucial report drafting stages, is very likely to miss expertise relevant to understanding significant issues for a particular chemical. One method that may warrant consideration is the model used by other scientific bodies (e.g., EPA's Science Advisory Board): to have a core group of standing expert scientists who serve as members of the Expert Panel, and to augment the Expert Panel, as needed, with additional experts who have either knowledge of the science for that chemical, or expertise in a germane discipline needed for the review of a specific chemical.

4. Clarifying the Listing/Delisting Criteria

Adopting the variant of the CERHR process discussed above would go a very long way to assuring the scientific quality of the RoCs. NTP should address one other substantive matter, however: clarifying its listing/delisting criteria for the RoC. Among the most important judgments to be made in issuing the RoC is whether the weight of the scientific evidence is sufficient to conclude that a substance is "known to be a human carcinogen." Such a classification will greatly intensify the level of regulatory and public concern surrounding exposure to the substance, and therefore the determination should be based on careful and thorough analysis. Yet, in contrast to other agencies and scientific bodies, NTP has to date not fully described or elaborated on the standards it will apply in judging whether the weight of the

available scientific data are sufficient to demonstrate a causal relationship between exposure to the substance and human carcinogenicity.

ACC urges NTP to clarify its listing/delisting criteria used for the RoC. Specifically, a "known to be a human carcinogen" determination should only be made if there is sufficient evidence of carcinogenicity from epidemiological studies that indicates a causal relationship between exposure to the agent, substance or mixture and human cancer. Mechanistic or other scientific information should not be used to bolster insufficient epidemiological evidence in an effort to satisfy the "known to be a human carcinogen" criteria.

For many years, NTP relied exclusively on epidemiological studies to satisfy its "known to be a human carcinogen" criteria. Regrettably, NTP modified its criteria in 1996 to allow mechanistic information to be used to shore up insufficient epidemiological studies. By expanding its criteria in this manner, NTP rendered effectively meaningless the distinction between "known to be a human carcinogen" and "reasonably anticipated to be a human carcinogen," thus frustrating the legislatively mandated distinction between the two. For example, currently, a substance for which NTP has limited human epidemiology data and relevant mechanistic data could be classified as either "known" or "reasonably anticipated." A substance for which there is limited epidemiological data and relevant mechanistic data should, at most, only be classified as "reasonably anticipated to be" and not "known to be a human carcinogen." Otherwise, this NTP policy results in the same regulatory priority being given to substances with vastly different weights of evidence. There should be clear policy distinction between determinations based on strong human epidemiological evidence and determinations that are based primarily on mechanistic data and inference. Maintaining a clear distinction between the two listing determinations is sound public policy. Such a distinction allows the scientific and public health communities, as well as regulators, to prioritize limited resources for the purposes of conducting research and protecting public health.

In addition, NTP should consider whether another classification is warranted in addition to "known" and "reasonably anticipated". There may be instances where the overall weight of the scientific evidence falls short of both criteria. As it now stands, there may be a tendency to "force" a classification into "reasonably anticipated" when the available scientific evidence may actually be much less. In this respect, a multiple level classification system, with appropriately worded text descriptions, would seem to offer a much better opportunity to fully and accurately communicate to the public the scientific evidence for such a substance with limited data -- in a manner that transparently reflects the true degree of confidence in the scientific data and evaluations. Clearly, a weight of the evidence approach is needed, particularly when there are multiple studies of varying quality that are not consistent. The criteria NTP develops and applies need to be explicit, transparent to stakeholders/public, and applied uniformly across substances and across time.

5. Conclusions

NTP is to be commended for seeking input on ways to improve the RoC listing and delisting process. ACC believes NTP should consider implementing changes which enhance the scientific quality of the review documents; to foster scientific dialog among subject matter experts; and to increase opportunities for meaningful stakeholder/public input. ACC has suggested that NTP consider adapting the CERHR process for the RoC. Implementing a more open and transparent process, such as that recommended, should result in higher quality scientific documents, greater opportunities for independent experts to meaningfully participate and therefore improved decision-making.

ACC appreciates the opportunity to offer both substantive and procedural recommendations for enhancing the scientific quality and credibility of the RoC. ACC appreciates your consideration of these comments and recommendations. If you or NTP staff have any questions on these comments or related matters, please contact Dr. Richard Becker by phone at 703/741-5210 or by e-mail at Rick_Becker@AmericanChemistry.com.

Sincerely,

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Figure 1. The CERHR Process

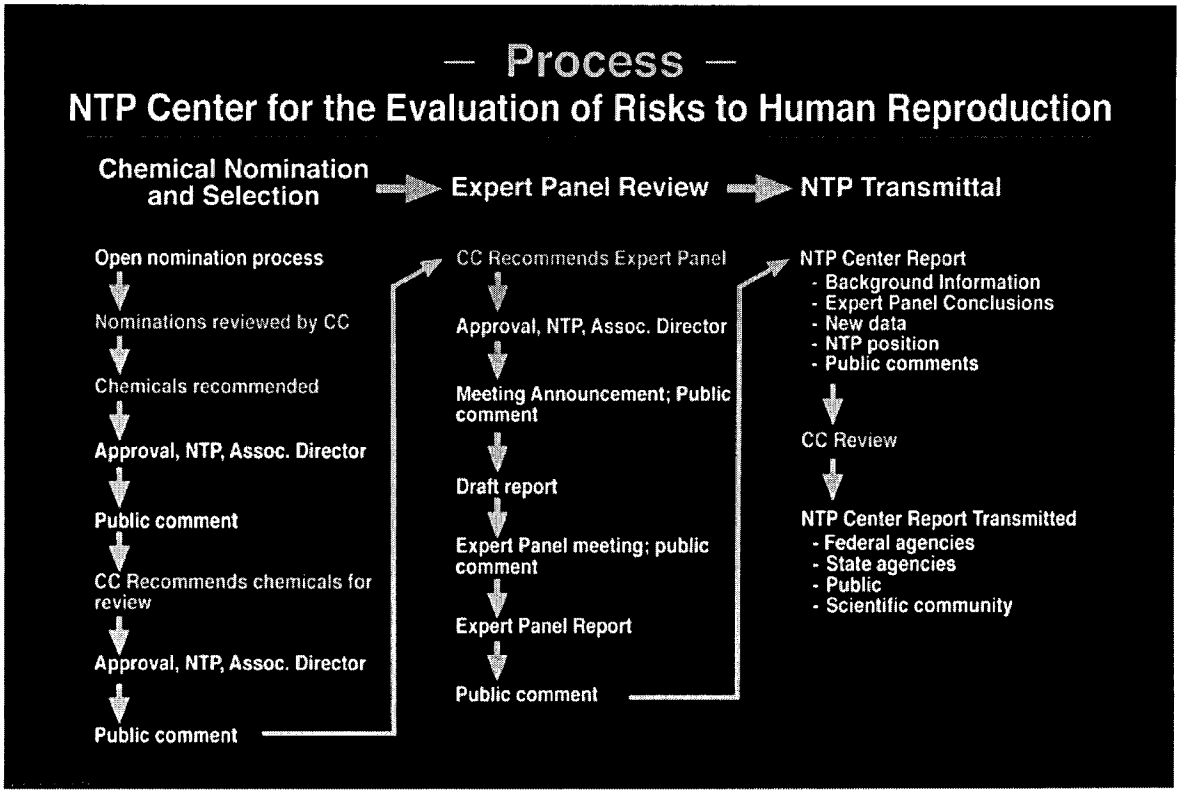

Figure 2
Recommended Process for Strengthening the RoC